REMARKS

I. Claim status

Claims 25-27, 44-50, 53-55, 57-64, 66-77, and 79-82 are pending in this application. Claims 83-91 have been added. Support for the amendments and new claims can be found throughout the specification and original claims. No new matter has been added.

II. Rejection under 35 U.S.C. § 112, first paragraph

Claims 25-27, 66-77, and 79-82 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled because the specification does not enable any person skilled in the art to use the invention commensurate in scope with the claims. Applicants traverse the rejection because the full scope of the claims is more than adequately enabled by the specification.

Gene Therapy is not Antisense Therapy

The Office Action appears to mistakenly perpetuate a fundamental confusion between antisense and gene therapies. The Office Action incorrectly states, for example, that "[t]reatment with ***antisense*** nucleic acids is a new and developing art involving ***gene therapy***..." (page 4). Antisense therapy and gene therapy are known in the art to be quite different. While both methods involve the introduction of nucleic acids into cells, the similarities stop there. Among many differences, antisense therapy involves the introduction of relatively short nucleic acids (e.g., oligonucleotides typically having 7-50 nt) into cells whereas gene therapy requires the introduction of relatively long nucleic acids (e.g., 500 bp or more) that often encode a particular gene product. Additionally, antisense therapy involves sequence specific interactions of introduced nucleic acids, whereas gene therapy involves integration and expression of introduced nucleic acids. It is well known by the very different natures of antisense therapy and gene therapy that the advantages or difficulties associated with one cannot be transferred to the other. Thus,

the Office Action has mistakenly equated gene therapy with antisense therapy to show alleged non-enablement of the claims.

The Specification Teaches Multiple Uses

Applicants respectfully point out that enablement is satisfied if the specification discloses ***at least one*** method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims. *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970) (emphasis added). Additionally, if multiple uses for an invention are provided in the specification, an enablement rejection should include an explanation and evidence as to why the specification fails to enable each disclosed use. See, e.g., M.P.E.P. 2164.01(c).

The Office Action appears to improperly assert that the claims are non-enabled because the specification fails to teach "a method of treatment" using the disclosed formulations and methods. While Applicants respectfully assert that the specification more than adequately teaches methods of treatment using the disclosed formulations and methods, it is pointed out that the specification describes numerous ***other*** uses that are commensurate in scope with the claims (see page 33 to 35). For example, the claimed "method of enhancing penetration" and "method of delivering an antisense nucleic acid" can be used to ***study the function of one or more genes in an animal*** (see page 33, line 28 to page 34, line 8). In fact, ***the Office Action admits that the claims are enabled for this use*** (page 3, ¶ 8). Further, the Office Action offers no reasoning or explanation for why the disclosure pertaining to this use is not enabling for the entire scope of the claims. Indeed, using the claimed subject matter to study of the function of one or more genes bears a more than reasonable correlation to the entire scope of the claims. Such a use cannot be disregarded, and thus, according to the Office Action's own admission, enablement is satisfied because the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims.

The Claims are Further Enabled for Methods of Treating

Although the claims are well enabled because the specification teaches how to make and use the claimed formulations and methods for studying the function of one or more genes in an animal, contrary to the assertions of the Office Action, the claims are also enabled for methods of treatment.

The enablement requirement of 35 U.S.C. § 112 mandates that the specification teach those skilled in the art how to make and use the claimed invention without undue experimentation. *See In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The test of enablement is ***not*** simply whether experimentation would have been necessary, but whether such experimentation would have been ***undue***. *See In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See Wands*, 8 U.S.P.Q.2d at 1404. Routine experimentation does not constitute undue experimentation.

The Office Action incorrectly asserts that the claims are non-enabled because treatment with nucleic acids is highly unpredictable, requiring undue experimentation. The Office Action cites Gewirtz, et al., *Proc. Natl. Acad. Sci. USA*, **1996**, *93*, 3161; Gura, *Science*, **1995**, *270*, 575; Stull, et al., *Pharmaceutical Research*, **1995**, *12*, 465; Agrawal, et al., *Molecular Medicine Today*, **2000**, *6*, 72; and Branch et al., *TIBS*, **1998**, *23*, 45 in support of its erroneous conclusion that treatment with nucleic acids is unpredictable. These references are insufficient to represent the broad area of antisense technology as unpredictable and do not reflect the state of the art as a whole at the time of filing. To illustrate, numerous references, many of which were published at the time of the above references, are provided below which show the ***successful*** and ***predictable*** use of antisense therapy.

As evidence of the ***predictable*** state of the art of antisense technology, Applicants herewith submit selected chapters form a book entitled *Antisense Drug Technology* (Marcel Dekker, Inc., (2001)). *Antisense Drug Technology* is replete with routine instructions and guidelines that can be used by a skilled practitioner to synthesize antisense oligonucleotides capable of binding target nucleic acids. For example, Chapter

5, entitled "Methods of Selecting Sites in RNA for Antisense Targeting," and the supporting references cited therein, illustrate that those skilled in the art do indeed consider antisense oligonucleotide chemistry to be predictable. For example, page 111, states that "[o]ne attraction of antisense technology is that high specificity can be achieved." The references that are citied in support of this statement, *i.e.*, references 11, 63, and 64, were published from 1994 to 1999. Accordingly, Chapter 5 of *Antisense Drug Technology*, along with the supporting references cited therein, teach that the state of the art of antisense oligonucleotide chemistry is indeed predictable and that those skilled in the art would not have had to partake in undue experimentation to achieve binding specificity.

Likewise, Chapter 7 of *Antisense Drug Technology* entitled "Suborgan Pharmacokinetics" and the references listed therein teach that the efficacy and safety of certain oligonucleotides in various animal models and in the clinical setting have been well documented (p.155). Chapter 7 further teaches that, in various animal models, not only can oligonucleotides be given directly without a carrier, but that such oligonucleotides are consistently (*i.e.*, ***predictably***) and unequivocally localized within the cells of various organs. Chapter 8 summarizes the art with respect to modulating the activity or production of proteins with respect to human subjects. Accordingly, Chapters 6 and 8 of *Antisense Drug Technology*, along with the supporting references cited therein, teach that the state of the art of antisense oligonucleotide chemistry is indeed predictable and that those skilled in the art do not have to partake in undue experimentation to modulate the production or activity of a protein in an organism, thus directly contradicting the allegations of non-enablement in the Office Action.

Another reference demonstrating the predictability of antisense technology is Whitesell *et al., Antisense Res. Dev.* (1991) 1:343-50 (hereinafter referred to as "Whitesell"). Whitesell teaches that those skilled in the art as far back as 1991 successfully performed *in vivo* modulation of N-myc expression in mice. Similarly, Mirabelli *et al., Anti-Cancer Drug Des.* (1991), 6, 647-661 ((hereinafter referred to as "Mirabelli") evidences the state of the art as far back as 1991. At page 651, fourth full paragraph, Mirabelli notes that "the therapeutic indexes of phosphorothioate

oligonucleotides appear to be quite high" and that "certain phosphorothioates . . . are extremely well tolerated in animals." Accordingly, Whitesell and Mirabelli provide evidence that as far back as 1991, one skilled in the art would not have to conduct undue experimentation to modulate the production or activity of a protein in an organism.

Yet another reference demonstrating the state of the art is *Ann. Rev. Pharmacol. Toxicol.* 1992, 32:329-76 ((hereinafter referred to as "Crooke"). Crooke is a 1992 review of the art and, at page 342, provides evidence that those skilled in the art were conducting *in vivo* pharmacokinetic data in mice and rats.

Still another reference is Cossum *et al.*, *The Journal of Pharmacology and Experimental Therapeutics* (1993) 267:1181-1190 ((hereinafter referred to as "Cossum"). Cossum discusses non-antisense effects and ways to avoid them *in vivo* by not using doses that are significantly greater than the antisense effective dose. Thus, by 1993, the skilled artisan knew how to avoid non-specific effects. Moreover, Cossum evidences that, by 1993, those skilled in the art were delivering antisense oligonucleotides *in vivo* where the only carrier was a phosphate buffer.

Moreover, a handful of oligonucleotide antisense molecules have, in fact, successfully completed phase III trials and been FDA approved. For example, the oligonucleotide antisense drug Fomivirsen (ISIS Pharmaceuticals, Inc. ("ISIS"), the assignee of the instant application) was approved for treatment of cytomegaloviral-induced retinitis by the FDA in 1998. The Investigational New Drug Application ("IND") for Fomivirsen was filed with the FDA back in 1993. Many other oligonucleotide antisense drugs are currently involved in clinical trials (*see, e.g.*, Tamm *et al.* (the Lancet (2001) 358:489-497 at 490)).

Significantly, a search of the art of antisense oligonucleotides reveals approximately 17,000 references that comprise the "state of the art" of antisense oligonucleotide chemistry. Given the wealth of information pertaining to antisense technology, the Office Action has clearly ignored the state of the art ***as a whole*** and has mischaracterized it as unpredictable by selecting only a few references that might support such an assertion.

Already of Record

Applicants also respectfully note that, in addition to the references mentioned above, numerous other references have already been made of record which show enablement of the claims, such as with respect to methods of treatment. For example, Applicants have provided, in connection with the Response dated December 20, 2000, 1) Monia, *et al.*, *Nature Med.*, **1996**, *2*, 668; 2) Oberbauer, *et al.*, *Proc. Natl. Acad. Sci. USA*, **1996**, *93*, 4903; 3) Monia, *et al.*, *Proc. Natl. Acad. Sci. USA*, **1996**, *93*, 15481; 4) Cucco, *et al.*, *Cancer Res.*, **1996**, *56*, 4332; 5) Offensperger, *et al.*, *Antisense Therapy of Hepatitis B Virus Infection*, 1996, Agrawal Ed., Humana Pres Inc., Tolowa, NJ, pp. 143-158; 6) Sun, *et al.*, *Br. J. Pharmacol.*, **1996**, *118*, 131; 7) Neurath *et al.*, *Nature Med.*, **1996**, *2*, 998-1004; 8) Leonetti, *et al.*, *J.N.C.I.*, **1996**, *88*, 419, and 9) Del Bufalo, *et al.*, *Br. J. Cancer*, **1996**, *74*, 387. These references show both the successful enhancement of oligonucleotide penetration across the alimentary canal and treatment of an animal. Each reference further demonstrates successful administration of pharmaceutical nucleic acids via the bloodstream or local administration. Each of these references shows that oligonucleotides administered to the bloodstream, in fact, reach their target destinations as well as have their intended effects on the target. This plethora of references demonstrates that methods of treatment using antisense molecules were routine in the art at the time of filing, and therefore, no undue experimentation is needed to practice the invention.

Declaration of Dr. Mark K. Wedel

The Office Action incorrectly fails to give full consideration of the evidence provided in the Declaration of Dr. Mark K. Wedel ("Wedel declaration") which shows predictability of antisense technology and enablement of the claims. The Office Action inappropriately dismisses the Wedel declaration because the declaration is silent as to the particular antisense formulation administered to patients in the reported clinical study. Applicants respectfully assert that absence of formulation details is not relevant to the purposes of the declaration. The Wedel declaration is provided to show, *inter alia*,

predictability of antisense technology regardless of formulation. Thus, absence of formulation details is insufficient reason to disregard the evidence provided therein.

The Office Action also alleges that the data accompanying the Wedel declaration in Exhibits D, E, and F, is "uninterpretable" as provided. First, even if the appended graphs were "uninterpretable" (which they are not), the data is explained in the body of the declaration (see, e.g., paragraphs 8-11). Thus, "uninterpretable" data cannot be a valid reason for dismissing the evidence provided in the declaration. Second, the data provided in Exhibits D, E, and F is ***not*** "uninterpretable," especially in light of the descriptions of the experiments and results provided in the body of the declaration. The Office Action provides no indication as to what is unclear about the graphical data in Exhibits D, E, and F, and incorrectly disregards the evidence provided in the declaration.

Accordingly, Applicants respectfully request reconsideration of the evidence provided in the Wedel declaration with respect to predictability of antisense technology and enablement of the claims.

Request for Withdrawal of Rejection

Because the specification teaches how to make and use the claimed subject matter, such as for methods of treatment and/or studying the function of one or more genes in an animal, and any required experimentation would not be undue, the full scope of the claims is enabled. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 112, first paragraph

II. The Claims are Novel

Claims 61 and 62 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Pat. No. 5,707,648 ("Yiv"). Applicants respectfully traverse the rejection because Yiv fails to teach every element of the claims.

The standard for anticipation under §102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Yiv fails to anticipate the compositions of claims 61-62 because Yiv fails to

disclose, *inter alia*, a nucleic acid with a modified nucleobase or a modified sugar residue. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 102(e).

III. The Claims are Not Obvious

Claims 25-27, 44-50, 53-55, 57-64, 66-73, 75-77, and 79-82 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Yiv in view of U.S. Pat. Nos. 5,843,738 ("Bennett") and/or 5,948,898 ("Dean"). Applicants traverse the rejection because *prima facie* obviousness has not been established.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992).

The Office Action has not established *prima facie* obviousness because legally sufficient motivation to combine the references has not been shown. For example, the Office Action incorrectly asserts that motivation to combine Yiv and Bennett arises from the teaching that an "antisense nucleic acid... is useful and desirable for decreasing the expression of a cellular adhesion protein or the rate of cellular proliferation." This does not provide a reason for why one skilled in the art would combine a reference directed to antisense therapy (Bennett) with a reference directed to oral delivery of macromolecular, preferably proteinaceous, active agents, (Yiv) to produce the claimed invention (e.g., a composition containing a nucleic acid and at least two fatty acids). Thus, motivation is insufficient to combine Yiv and Bennett.

Additionally, the Office Action incorrectly asserts that motivation to combine Yiv and Dean arises from the teaching of the "desirable and beneficial increase in affinity of the antisense for its target and the increased resistance to nuclease" upon specific modifications of the antisense nucleic acid (e.g., a 5-methyl-cytosine substitution). However, as discussed above, this alleged teaching does not provide a reason for why one

skilled in the art would combine a reference directed to antisense therapy (Dean) with a reference directed to oral delivery of macromolecular, preferably proteinaceous, active agents (Yiv) to produce the claimed invention (e.g., a composition containing a nucleic acid and at least two fatty acids). Thus there is no legally sufficient to combine Yiv and Dean.

Moreover, when assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a whole without undue emphasis on those features that would support a finding of obviousness. *In re Wesslau*, 147 U.S.P.Q. 391 (C.C.P.A. 1965) (it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art).

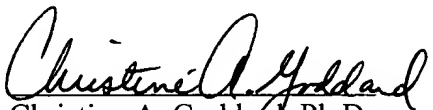
In the present case, the Office Action appears to have improperly "picked and chosen" from the cited references to allegedly produce the claimed subject matter. For example, the Office Action has not provided reasoning or motivation as to why one skilled in the art would select fatty acids from the numerous formulation components recited in Yiv, Bennett, and Dean. The Office Action has further not provided reasoning or motivation as to why one skilled in the art would select a bile salt from the numerous recited ingredients of the references, nor has motivation been indicated for combining it with fatty acids. Further, the Office Action has not provided reasoning or motivation as to why one skilled in the art would select capric and lauric acids over the numerous other fatty acids and formulation ingredients recited. Thus, legally sufficient motivation has not been shown to make a *prima facie* case of obviousness.

Because the Office Action fails to provide legally sufficient motivation for the proposed combinations of references and improperly picks and chooses from among the many ingredients reported in Yiv, Bennett, and Dean, providing no motivation for the necessary selections, *prima facie* obviousness cannot be established. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims.

IV. Conclusion

In view of the foregoing, Applicant submits that the claims as amended are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Respectfully submitted,



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Date: April 21, 2003

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